

Rapid Deterioration of HIV Co-infected Patients Waiting for Liver Transplantation Is Not Predicted by MELD

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HAART therapy has significantly decreased the morbidity and mortality associated with HIV infection and, as a result, people infected with HIV are no longer dying from progression of HIV to AIDS. Unfortunately, an increasing number of co-infected patients are dying from complications of liver failure. Liver disease is now the leading cause of death for HIV-positive patients co-infected with hepatitis C and a major cause of death for HIV/HBV co-infected patients.¹ As a result of the increasing demand for liver transplantation in HIV-positive people and recognition of improved survival associated with HAART, a number of transplant centers are proceeding with liver transplantation in selected patients with well-controlled HIV. Multiple small studies in the era of HAART suggest that patient and graft survival rates are similar to those in HIV-negative recipients.²⁻¹⁰ It is on this background that Ragni et al.¹¹ in this issue of *Liver Transplantation* demonstrate significantly shorter pretransplantation survival in HIV-positive patients listed for liver transplantation compared with HIV-negative subjects, despite equivalent Model for End-Stage Liver Disease (MELD) scores at the time of listing. Furthermore, the shortened pretransplantation survival times were primarily associated with death related to infection/sepsis in a subset of the HIV-positive candidates.

Ragni et al.'s findings are highly relevant, in that this is the first documentation of a more rapid demise of the co-infected HIV liver transplant candidates that has been observed on waiting lists at an increasing number of transplant centers. The parameters that have proven to be predictive for poor outcome in the MELD system (INR, bilirubin, and creatinine) failed to predict the poorer outcome in the subset of HIV-positive patients who succumbed to infection/sepsis. CD4 counts at the time of listing were also unable to distinguish the subset of HIV-positive patients with poor outcomes. The higher incidence of sepsis-related death in HIV-positive people with liver insufficiency as compared to their HIV-negative counterparts on the liver transplant waiting list could be predicted on the basis of the multiple immunologic and metabolic insults present in the co-

infected patient with liver insufficiency. In addition to the impaired detoxification capacity of the damaged liver, the co-infected patient is further compromised by the immune defects associated with HIV as well as the hepatotoxicity of several of the antiretroviral agents comprising HAART. Therefore, the documentation of increased sepsis/infections leading to decreased cumulative survival rates of HIV co-infected candidates on liver transplant waiting lists should come as no surprise. However, the issue of what can be done to improve the survival of the HIV co-infected liver transplant candidate remains unresolved.

Ragni et al. stress the importance of early referral of the HIV co-infected patient, and the importance of this cannot be underestimated. There are multiple barriers that can delay the evaluation process leading to activation as an acceptable candidate, and Ragni et al.'s report makes it clear that this group of patients cannot afford these delays. It should be emphasized that these patients must meet the same standards as all liver transplant recipients, including a prolonged period of abstinence from alcohol and narcotics, sufficient rehabilitation, and demonstration of social support. Since HIV positivity is still perceived as a contraindication to transplantation by a significant percentage of the medical community, these issues have not been adequately dealt with by the time of referral. The problems with late referral are further exacerbated by the inherent complexity in caring for HIV/HBV and HIV/HCV co-infected patients. Many of these patients are disenfranchised from essential medical care as a result of poor insurance coverage. Even when appropriate medical consultation is obtained, the hepatologist will defer to the HIV specialist, the HIV specialist defers back to the

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hepatologist, and ultimately the patient ends up at a transplant center with very advanced liver disease. The necessity for synchronized medical management has become apparent in several HIV/HBV co-infected patients referred to our transplant center with severely decompensated liver function. A majority of HIV-positive patients on HAART include epivir (nucleoside analogue) as a component of the regimen. Unfortunately, epivir (lamivudine) is also the primary anti-viral agent used to suppress HBV, and acute decompensation from an HBV flare related to the development of resistance in the HIV/HBV-infected patients has been observed with multiple referrals. Following the appropriate treatment for HBV-lamivudine resistance (adefovir or tenofovir), the acute flare and decompensation resolves and the patient no longer requires transplantation.

The NIH multicenter trial evaluating the safety and efficacy of solid organ transplants in people with HIV (<http://www.hivtransplant.com>) requires liver transplant candidates to have CD4 counts greater than 100, the absence of current opportunistic infections, as well as documentation that HIV can be suppressed with an anti-retroviral regimen. These criteria were established to select patients who were expected to tolerate immunosuppression without significant HIV disease progression. In the early experience of solid organ transplantation in people with HIV, there has not been any significant HIV progression using these entry criteria, and these criteria continue to be used to determine eligibility at most centers. Unfortunately, by the time the liver function deteriorates to the point where the MELD score is sufficiently high for allocation, the HIV-positive candidate no longer meets the entry criteria applied by most transplant centers. Although MELD is continually evolving, it is unlikely that additional MELD points for HIV-positive patients will become part of the standardized point system. The data presented in by Ragni et al. might be helpful in guiding the regional review boards to consider some additional MELD points for the co-infected patients. Since it is unlikely that co-infected patients will receive additional allocation points in the MELD system in a consistent manner, it is important to pursue alternative sources of donor livers that would facilitate earlier transplantation.

In light of the poorer survival for the co-infected patient activated on the liver transplant waiting lists, the utilization of living donor liver grafts (right lobe) has been one solution to transplantation for the co-infected patient at a lower MELD score. These advantages must be weighed against the morbidity to the living donor of the right lobe, as well as the increased risks to the recip-

ient of hepatic artery thrombosis and biliary tract complications associated with transplanting the right lobe. The possibility for exacerbating HCV recurrence in the setting of regeneration remains a theoretic problem with living donation, although the significance of this problem remains controversial. Another potential source of deceased donor organs come from donors considered to be at a "high infectious risk." These organs are serologically negative for HIV, HBV, and HCV but are procured from a deceased donor who may have engaged in behavior putting them at risk for acquiring HIV. Although several of these high infectious risk donors have been used for kidney transplantation into HIV-positive recipients (where dialysis is an option for the HIV-negative recipient), these organs are generally accepted for all liver transplant recipients, regardless of HIV status. It should be emphasized that the use of high infectious risk donors is significantly different than the use of known HIV-infected donors. Because the use of an organ from a known HIV-positive donor carries the risk of super-infection with drug-resistant or a more virulent strain of HIV, we have not considered the use of these organs. There have been some recent attempts at the government level to permit the procurement of organs from deceased HIV-positive donors for utilization in HIV-positive recipients, recognizing the increase in number of HIV-positive recipients on both kidney and liver waiting lists. Although we have been opposed to the use of these organs because of concerns related to super-infection with a more virulent strain, the alternative of waiting on the list until a sufficiently high MELD score is obtained for a "standard" donor may not be an option for the HIV positive co-infected patient.

A final unspoken hurdle to widespread application of liver transplantation in the HIV co-infected patient is the continued concern for HIV transmission to the surgeon and health care team during technically challenging liver transplants. Although the risk of HCV transmission with a needle-stick is seven-fold that of HIV transmission, and the fact that the majority of HIV positive patients undergoing transplantation have undetectable HIV, the fear of HIV transmission has prevented several surgeons from embracing liver transplantation in co-infected patients. In a recently published survey, Halpern et al.¹² found the majority of transplant surgeons were willing to perform transplantations involving HCV-infected patients but not HIV-infected patients, even though they believed HCV and HIV transplant recipients had similar posttransplantation survival. It is imperative that clinicians make every attempt to suppress HIV prior to liver transplantation if

HAART can be tolerated, in order to further reduce the risk of transmission in the event of a needle stick. The determination of postexposure prophylaxis (PEP) regimens should be standard during the pretransplantation evaluation, taking into account the HIV resistance patterns present in the recipient. PEP medications and consultations should be available immediately to any exposed health care worker. Minimization of transmission risks as well as attention to optimal PEP will reduce the unspoken anxiety among health care workers that may indirectly limit prompt access to liver transplantation for the co-infected patient.

In summary, the findings of Ragni et al. confirm the significantly decreased survival of the HIV co-infected patient on the liver transplant waiting list, and emphasize the importance of early referral to permit a complete evaluation and activation for transplantation.¹¹ The results from multiple pilot trials suggest the early outcomes following liver transplantation in co-infected patients are comparable to those of HIV-negative liver recipients. Since it is unlikely that regional review boards will routinely approve additional MELD points to the HIV co-infected patients, the aggressive pursuit of "infectious high-risk" deceased donor livers as well as living donor liver transplants will be important to expedite transplantation prior to life-threatening decompensation. Similarly, synchronized multi-special care along with early referral will help to minimize the number of deaths on the waiting lists and facilitate excellent outcomes following liver transplantation in this deserving group of recipients.

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